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NPL REPORT IR 48

CROSS CALIBRATION OF ALANINE FOR SCANNED PROTON BEAMS

HUGO PALMANS, ANTONIO CARLINO, CLARE GOULDSTONE AND PETER SHARPE

JULY 2018

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Hugo Palmans[1,2], Antonio Carlino[2], Clare Gouldstone[1] and Peter Sharpe[1]

[1] National Physical Laboratory, Chemical, Medical and Environmental Science Department, Teddington, United Kingdom
[2] MedAustron Ion Therapy Center, Medical Physics Department, Wiener Neustadt, Austria

ABSTRACT

Alanine is a suitable dosimeter for absolute dosimetry, dose verification, end-to-end dosimetry and dosimetric audit of clinical proton beams. For establishing traceability to primary standards of absorbed dose to water, NPL's alanine dosimeter is calibrated in a ^{60}Co photon beam. The energy dependence of the alanine response in proton beams has been well understood but a systematic difference of about 2% between the alanine response in high-energy proton beams and its response in a ^{60}Co photon beams has been demonstrated. For this reason we propose to cross calibrate the alanine dosimeter in a high-energy proton beam for its use in any clinical proton beam. This report presents the results of the cross calibration of alanine detectors in a high-energy scanned proton beam at MedAustron. The cross-calibration establishes a value of the beam quality correction factor and its uncertainty. The report also details how the alanine dosimeters should subsequently be used in clinical proton beams different from the cross-calibration beam quality.

National Physical Laboratory

Hampton Road, Teddington, Middlesex, TW11 0LW

Approved on behalf of NPLML by

Graham Bass, Science Area Leader, Medical Radiation Science.

CONTENTS

1   INTRODUCTION

Alanine has been investigated in numerous studies as a suitable dosimeter for mixed charged particle fields [1–6]. At MedAustron it is used for dosimetric end-to-end testing, which consists of loading an anthropomorphic phantom with dosimeters and putting it through the entire treatment work flow as if it was a real patient. This procedure involves the entire logistic chain of patient treatment from CT imaging, treatment planning, patient setup and verification to beam delivery. In collaboration with the NPL, alanine is also being proposed as a tool for dosimetric audit of scanned particle beam facilities based on the dosimetric end-to-end tests developed at MedAustron. A pilot audit was performed [5] and the application to dosimetric end-to-end testing consolidated the basis for using alanine for dosimetric audit [6, 7].

The response of solid state detectors like films or alanine to a given absorbed dose depends explicitly on the type, the fluence and the energy of the particles which constitute the mixed radiation field. The response of an alanine pellet for a given radiation beam quality Q, representing the full charged particle spectrum of a mixed radiation field, can be expressed by its relative effectiveness $\overline{\eta}_{\text{alanine},Q}$ defined as:

$$\overline{\eta}_{\text{alanine},Q} = \frac{D_{\text{alanine},^{60}\text{Co}}}{D_{\text{alanine},Q}} \tag{1}$$

where $D_{\text{alanine},Q}$ is the absorbed dose to alanine in a proton beam of beam quality Q and $D_{\text{alanine},^{60}\text{Co}}$ is the absorbed dose to alanine in a ^{60}Co beam which yields the same detector response. The beam quality in proton beams is usually, and also in this report, characterized by a single-parameter beam quality specifier, the residual range, defined as the distance from the depth of measurement in water to the 10% point on the distal edge of the percentage depth dose distribution.

In the case that track overlapping effects on a microscopic level can be neglected, the relative effectiveness $\overline{\eta}_{\text{alanine},Q}$ can be calculated from the binned energy spectra of all charged particles in the radiation field as a dose-weighted average of the energy dependent relative effectiveness [1, 2, 4], $\eta_{\text{alanine},i}$, of each ion type, i:

$$\overline{\eta}_{\text{alanine},Q} = \frac{\sum_{i=1}^{n_{\text{proj}}} \int_{E_{\min,i}}^{E_{\max,i}} \phi_{E,i} \left(\frac{S}{\rho}\right)_{\text{alanine},i} \eta_{\text{alanine},i} dE}{\sum_{i=1}^{n_{\text{proj}}} \int_{E_{\min,i}}^{E_{\max,i}} \phi_{E,i} \left(\frac{S}{\rho}\right)_{\text{alanine},i} dE} \tag{2}$$

This expression will form the basis of the calculation of a beam quality correction factor for alanine in Section 5. It was also used by Carlino *et al* [7] for dosimetric end-to-end testing at MedAustron. In that study, however, a systematic discrepancy of about 2% was observed between alanine dosimetry

and ionization chamber dosimetry, after correcting the alanine response with equation (2). Even though this discrepancy is well within the overall relative uncertainties of both dosimetry systems (4% for the ionization chamber dosimetry and 6% for the alanine dosimetry at 95% confidence level) it was consistently observed for all 230 alanine dosimeters used and indicates that there is systematic discrepancy between alanine and ionization chamber dosimetry hidden within the overall uncertainty budgets. To provide consistency with ionization chamber dosimetry, it was thus proposed to cross-calibrate alanine in a high-energy proton beam against an ionization chamber [7]. This approach is equivalent to the use of an overall beam quality correction factor that accounts for the different absorbed dose to water calibration coefficients of alanine in the ^{60}Co calibration beam and in the high-energy proton beam.

In this report, a formalism is established to define a beam quality correction factor for alanine, to cross-calibrate alanine dosimeters against a Farmer-type ionization chamber in a high-energy proton beam and to use alanine as a dosimeter in mixed radiation fields. Furthermore, the experimental setup to determine the beam quality correction factor for alanine in the cross-calibration field is described and the results with their uncertainty presented. An experimental example of the subsequent application of alanine in a dosimetric end-to-end test for a clinical proton beam is also shown.

2   FORMALISM

2.1 ABSORBED DOSE TO WATER DETERMINATION USING AN IONIZATION CHAMBER

Absorbed dose to water in the single layer scanned field is determined using a Farmer ionization chamber according to the IAEA-TRS398 formalism [8]:

$$D_{\text{w},Q_{\text{cross}}}^{\text{Farmer}} = M_{Q_{\text{cross}}}^{\text{Farmer}} N_{D,\text{w},Q_0}^{\text{Farmer}} k_{Q_{\text{cross}},Q_0}^{\text{Farmer}} \tag{3}$$

where Q_{cross} is the beam quality of a 179.2 MeV unmodulated beam at a reference depth $z_{\text{ref}} = 2$ cm in water with a residual range of 19.4 cm, $N_{D,\text{w},Q_0}^{\text{Farmer}}$ is the absorbed dose to water calibration coefficient of the Farmer in the calibration beam quality Q_0 (^{60}Co, so in principle the short notation omitting Q_0 from the equations could be used), $M_{Q_{\text{cross}}}^{\text{Farmer}}$ is the Farmer ionization chamber reading corrected for influence quantities (atmospheric pressure, temperature, humidity, polarity effects and ion recombination) and $k_{Q_{\text{cross}},Q_0}^{\text{Farmer}}$ is the beam quality correction factor for the Farmer in the cross-calibration beam quality.

2.2 CROSS CALIBRATION OF ALANINE

A similar expression as Equation (3) can be proposed for dose to water in the cross-calibration beam quality obtained using alanine:

$$D_{\text{w},Q_{\text{cross}}}^{\text{alanine}} = M_{Q_{\text{cross}}}^{\text{alanine}} \, N_{D,\text{w},Q_0}^{\text{alanine}} \, k_{Q_{\text{cross}},Q_0}^{\text{alanine}} \qquad (4)$$

The product $M_{Q_{\text{cross}}}^{\text{alanine}} \, N_{D,\text{w},Q_0}^{\text{alanine}}$ is what the NPL provides as a ^{60}Co-reference value of absorbed dose to water, i.e., the dose to water that should be delivered at the measurement point in water by a ^{60}Co calibration beam to induce the same signal as the proton beam. The notation for this quantity is $D_{\text{w}}^{\text{Co-ref}}$ in this document.

The value of $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ derived from the cross-calibration is then obtained from Equations (3) and (4) using the condition that $D_{\text{w},Q_{\text{cross}}}^{\text{Farmer}} = D_{\text{w},Q_{\text{cross}}}^{\text{alanine}}$:

$$k_{Q_{\text{cross}},Q_0}^{\text{alanine}} = \frac{M_{Q_{\text{cross}}}^{\text{Farmer}} \, N_{D,\text{w},Q_0}^{\text{Farmer}} \, k_{Q_{\text{cross}},Q_0}^{\text{Farmer}}}{M_{Q_{\text{cross}}}^{\text{alanine}} \, N_{D,\text{w},Q_0}^{\text{alanine}}} \qquad (5)$$

2.3 ABSORBED DOSE TO WATER DETERMINATION USING ALANINE

For a pellet used at a beam quality Q, different from Q_{cross}, an additional beam quality correction factor, $k_{Q,Q_{\text{cross}}}^{\text{alanine}}$, is required:

$$D_{\text{w},Q}^{\text{alanine}} = M_Q^{\text{alanine}} \, N_{D,\text{w},Q_0}^{\text{alanine}} \, k_{Q_{\text{cross}},Q_0}^{\text{alanine}} \, k_{Q,Q_{\text{cross}}}^{\text{alanine}} \qquad (6)$$

From the formalism of Herrmann [3] or Ableitinger [5]:

$$k_{Q,Q_0}^{\text{alanine}} \approx \frac{1}{\overline{\eta}_{\text{alanine},Q}} \left[\left(\frac{\mu_{\text{en}}}{\rho} \right)_{\text{w}}^{\text{alanine}} \right]_{Q_0} \left[\left(\frac{s}{\rho} \right)_{\text{alanine}}^{\text{w}} \right]_Q \qquad (7)$$

where $\overline{\eta}_{\text{alanine},Q}$ is the relative effectiveness of alanine at the beam quality Q, $\left[\left(\frac{\mu_{\text{en}}}{\rho} \right)_{\text{w}}^{\text{alanine}} \right]_{Q_0}$ is the mass energy absorption coefficient ratio alanine to water at the calibration beam quality and $\left[\left(\frac{s}{\rho} \right)_{\text{alanine}}^{\text{w}} \right]_Q$ is the mass stopping power ratio water to alanine for the proton beam quality Q.

Similarly:

$$k_{Q_{cross},Q_0}^{alanine} \approx \frac{1}{\overline{\eta}_{alanine,Q_{cross}}} \left[\left(\frac{\mu_{en}}{\rho}\right)_w^{alanine}\right]_{Q_0} \left[\left(\frac{s}{\rho}\right)_{alanine}^w\right]_{Q_{cross}} \tag{8}$$

so

$$k_{Q,Q_{cross}}^{alanine} \approx \frac{k_{Q,Q_0}^{alanine}}{k_{Q_{cross},Q_0}^{alanine}} = \frac{\overline{\eta}_{alanine,Q_{cross}}}{\overline{\eta}_{alanine,Q}} \frac{\left[\left(\frac{s}{\rho}\right)_{alanine}^w\right]_Q}{\left[\left(\frac{s}{\rho}\right)_{alanine}^w\right]_{Q_{cross}}} \tag{9}$$

and given that the mass collision stopping power ratio water to alanine is almost independent of proton energy:

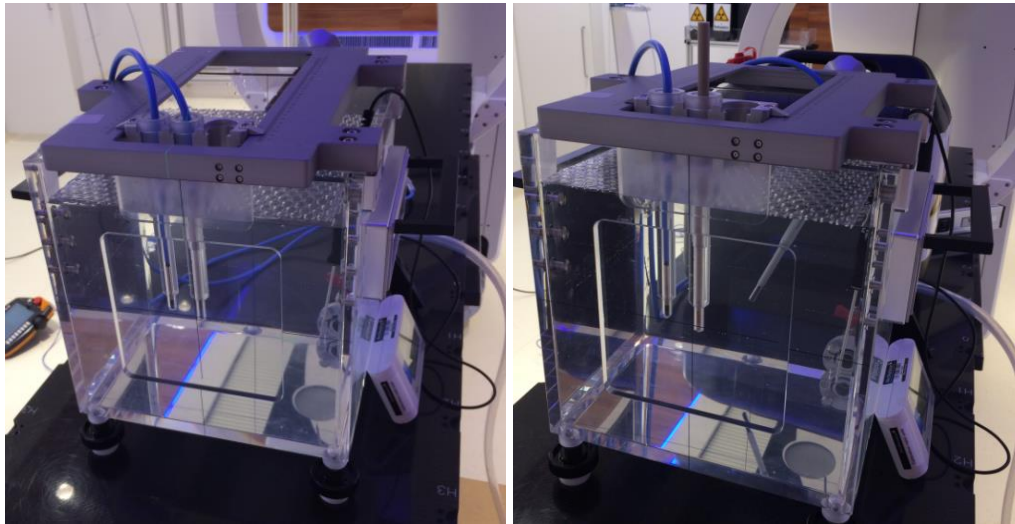$$k_{Q,Q_{cross}}^{alanine} \approx \frac{\overline{\eta}_{alanine,Q_{cross}}}{\overline{\eta}_{alanine,Q}} \tag{10}$$

3   EXPERIMENTAL DETERMINATION OF $k_{Q_{cross},Q_0}^{alanine}$

The cross-calibration of alanine was performed in a stationary water phantom MP1 (PTW, Freiburg) with a 3 mm thin PMMA entrance window. The only movable axis of the MP1 water phantom is in depth and the position can be read out with 0.1 mm resolution. The phantom was set up with the outer surface of the thin window at the isocenter. Two cross calibrations were performed on separate dates.

Since alanine pellets are hygroscopic they need to be waterproofed before inserting them into the water phantom. Customized holders were provided together with the alanine pellets by the NPL. The holders (F-type) have the same outer dimensions as the Farmer chamber and can be placed inside the same plastic sleeve commercially designed for the Farmer. In each F-type holder nine alanine pellets were positioned. An additional plastic rod of 15 cm can be screwed on the F-type holder to insert and remove it easily from the plastic Farmer sleeve. The same commercial Farmer sleeve was used for accurately positioning the F-type holder and the Farmer ionization chamber (TM30013) at the same measurement depth in water.

To perform the cross-calibration by the substitution method, both detectors were alternately irradiated in a single-layer scanned field of size 7 cm × 7 cm and nominal energy 179.2 MeV in the same sleeve, positioned at the clinical reference depth, z_{ref}, of 2.0 cm in water. In the first cross-calibration session this was done for dose levels of 8, 10, 12 and 16 Gy and during the second session only at 8, 10 and 12

Gy. The effective point of measurement of both detectors was positioned at the reference depth. For the Farmer ionization chamber this means that its reference point (the centre of the chamber) was positioned at a distance 0.75 times the inner radius of its cylindrical cavity (i.e., 0.23 cm) deeper in water than the reference depth. For the alanine pellet the centre of mass of the detector was positioned at the reference depth given that the mass density of alanine is not too different from that of water. The setup is illustrated in Figure 1.


Figure 1. Left: setup of the MP1 water phantom at isocenter with the Farmer chamber positioned along the central beam axis. Right: setup of the MP1 water phantom at isocenter with the F-type holder containing nine alanine pellets.

$k_{Q_{cross},Q_0}^{alanine}$ values were derived using Equation (5) with N_{D,w,Q_0}^{Farmer} determined at the NPL, $k_{Q_{cross},Q_0}^{Farmer} = 1.029$ from IAEA TRS-398 and D_w^{Co-ref} ($= M_{Q_{cross}}^{alanine} N_{D,w,Q_0}^{alanine}$) values provided by the NPL.

The $k_{Q_{cross},Q_0}^{alanine}$ values for the nine pellets per dose level are shown in Figure 2. These show that there is no general trend within each set of pellets and thus that the nine pellets can be assumed to be independent determinations of the alanine response for the same dose level.

The standard deviations of the four sets of nine pellets vary between 0.4% and 0.9% which is very consistent with the reproducibility of 5 cGy or 0.3% (whichever is larger) quoted for the NPL's therapy level alanine dosimetry service expressed as one standard deviation. This indicates that there is no substantial additional uncertainty resulting from lateral ripples and field non-uniformity.
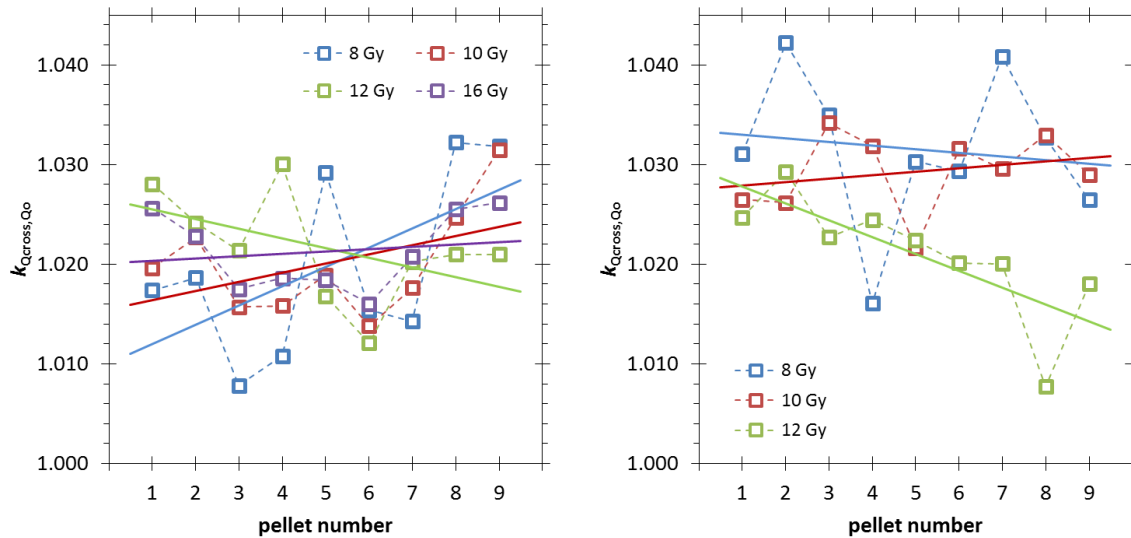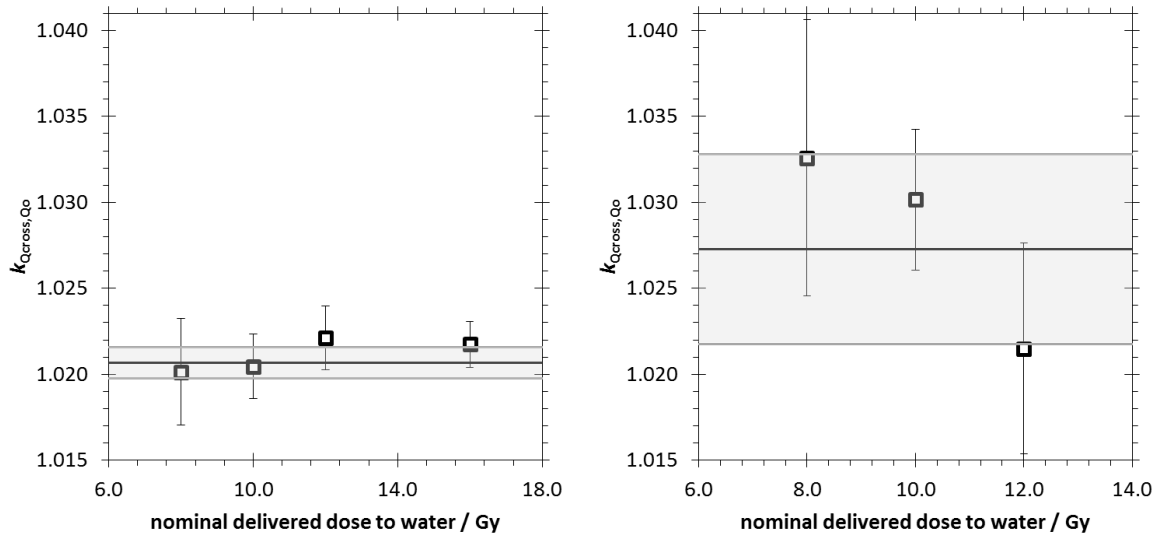
Figure 2. $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ values for all pellets, left: obtained from the first cross-calibration session and right: obtained from the second cross-calibration session. The solid lines represent linear fits for each set of 9 pellets at the same dose level.

The mean $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ values with their standard deviations of the mean are shown for each dose level in Figure 3 for both cross-calibration sessions. No significant trend as a function of dose level can be observed within the type-A uncertainties. The average and standard deviation of those mean $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ values are also presented as full black lines and shaded areas, respectively. Both cross calibrations are consistent given the standard deviations but it is obvious that the uncertainty in the second determination is considerably larger as in the first cross-calibration session.

In Figure 4, $D_{\text{w},Q_{\text{cross}}}^{\text{Farmer}}$ values determined for each nominal dose level with the Farmer ionization chamber by Equation (3) are plotted versus the mean of $D_{\text{w}}^{\text{Co-ref}}$ values determined by the NPL. The type-A uncertainties are too small to be visualized in this graph. From the linear fits (represented as $y = ax + b$), $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ can be derived as: $(ax + b)/x$ at 10 Gy dose level. In the case the fit is assumed to go through the origin $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ equals the slope (a) of the linear fit.

Table 1 presents the values of $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ based on the three methods outlined above with their corresponding uncertainties.

Figure 3. Mean $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ values (of nine pellets per dose level) as a function of nominal dose, left: obtained from the first cross-calibration session and right: obtained from the second cross-calibration session. The error bars represent type-A uncertainties. The horizontal full black line is the average and the grey shaded area represents the standard deviation of the values within one cross-calibration session.
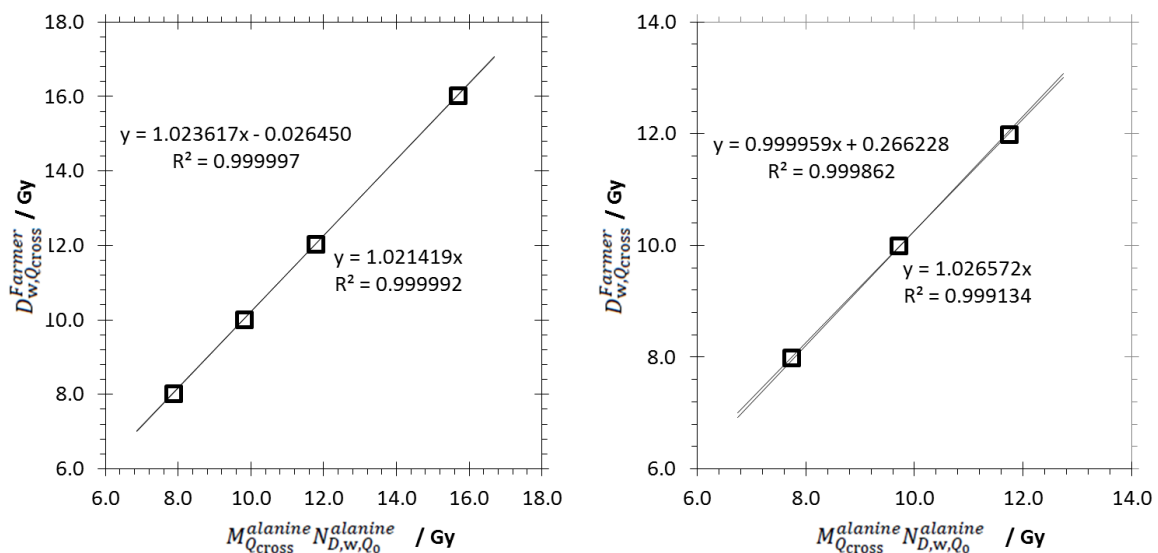
Figure 4. Values of the dose to water determined with the Farmer ionization chamber versus the mean values of $D_{\text{w}}^{\text{Co-ref}}$ ($= M_{Q_{\text{cross}}}^{\text{alanine}} N_{D,\text{w},Q_0}^{\text{alanine}}$) as determined by the NPL, left: obtained from the first cross-calibration session and right: obtained from the second cross-calibration session. The lines represent linear fits to the data with the equations shown next to them.

Table 1. Experimental values of $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ with uncertainties to provide consistency with IAEA TRS-398.

Method	Value ± standard uncertainty	
	First cross-calibration	Second cross-calibration
Average of four dose points	1.0207 ± 0.0050	1.0273 ± 0.0096
Linear fit (value at 10 Gy)	1.0210 ± 0.0060	1.0266 ± 0.0206
Slope of proportional fit	1.0214 ± 0.0045	1.0266 ± 0.0076

For the value derived as the average of the four dose points the standard deviation is added in quadrature with the overall uncertainty of Table 3. For the data that result from the linear regression analysis, the uncertainty on the fit coefficients is added in quadrature with the overall uncertainty of Table 3. For both calibration sessions the three results agree well within the estimated uncertainties. The results from both calibration sessions also agree within the uncertainties but the uncertainties for the second calibration session are considerably larger.

The average value of $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ from all six results is 1.024 ± 0.011 and the weighted average value is 1.022 ± 0.007. The uncertainties are determined by adding the combined uncertainty and the standard deviation of the six values (either unweighted or weighted) in quadrature. We opted to use the weighted data concluding that the best estimate of $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ to provide consistency with ionization chamber based reference dosimetry according to IAEA TRS-398 is:

$$k_{Q_{\text{cross}},Q_0}^{\text{alanine}} = 1.022 \pm 0.007$$

An equivalent interpretation of this value is that the absorbed dose to water calibration coefficient of alanine in the high-energy proton cross-calibration beam is 2.2% higher than in a ^{60}Co calibration beam corresponding well with the earlier quoted 2% discrepancy observed by Carlino *et al* [7]. Since theoretical models predict the relative effectiveness of alanine to be close to unity for high-energy protons [4], this means that either the beam quality correction factor for the ionization chambers, the stopping power ratio water-to-alanine in protons, the mass-energy absorption coefficient ratio water-to-alanine in the ^{60}Co calibration beam, perturbation factors for alanine pellets in proton beams or in the calibration beam or a combination of a number of these components is at the basis of this discrepancy.

4 UNCERTAINTY OF $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$

Given the experimental determination of $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ using Equation (5), the total uncertainty budget is summarized in Table 2 taking into account the reproducibility of the Farmer reading and setup (the latter due to non-uniformity of the beam and ripple effects), the reproducibility of the alanine reading (type-A uncertainty of 9 pellets per dose point), the uncertainty of the ratio between the Farmer and alanine calibration coefficients (these are largely correlated because they are traceable to the same primary standard) and the value of $k_{Q_{\text{cross}},Q_0}^{\text{Farmer}}$ as provided by IAEA TRS-398.

Other sources of reproducibility such as the different models used for the analysis and the long term variations of the beam delivery are not given but they are implicitly taken into account in the uncertainty estimates in the previous section based on the $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ values given in Table 1.

The aim of the cross calibration of alanine in a high-energy proton beam is, however, to provide consistency with ionization chamber based reference dosimetry as recommended by IAEA TRS-398. The uncertainty to provide this consistency should thus exclude the specific beam quality correction factor for the Farmer ionization chamber and is given in Table 3.

Table 2. Uncertainty budget for the experimental value of $k_{Q_{\text{cross}},Q_0}^{\text{alanine}}$ apart from reproducibility contributions due to the different models used and the different cross-calibration sessions.

Contribution	Relative standard uncertainty (%)	Source
$M_{Q_{\text{cross}}}^{\text{Farmer}}$	0.3	Type-A uncertainty and reproducibility of reference conditions (uniformity, ripples, etc.)
$M_{Q_{\text{cross}}}^{\text{alanine}}$	0.2	Type-A uncertainty of alanine readout (9 pellets)
$N_{D,\text{w},Q_0}^{\text{Farmer}}/N_{D,\text{w},Q_0}^{\text{alanine}}$	0.2	NPL calibrations (largely correlated)
$k_{Q_{\text{cross}},Q_0}^{\text{Farmer}}$	1.7	IAEA TRS-398
Total	**1.8**	**Combined uncertainty dominated by uncertainty of $k_{Q_{\text{cross}},Q_0}^{Farmer}$**

Table 3. Uncertainty on the experimental determination of $k^{\text{alanine}}_{Q_{\text{cross}},Q_0}$ to provide consistency with IAEA TRS-398 apart from reproducibility contributions due to the different models used and the different cross-calibration sessions.

Contribution	Relative standard uncertainty (%)	Source
$M^{\text{Farmer}}_{Q_{\text{cross}}}$	0.3	Type-A uncertainty and reproducibility of reference conditions (uniformity, ripples, etc.)
$M^{\text{alanine}}_{Q_{\text{cross}}}$	0.2	Type-A uncertainty of alanine readout (9 pellets)
$N^{\text{Farmer}}_{D,\text{w},Q_0} / N^{\text{alanine}}_{D,\text{w},Q_0}$	0.2	NPL calibrations (largely correlated)
$k^{\text{Farmer}}_{Q_{\text{cross}},Q_0}$	—	
Total	**0.4**	

5   CALCULATION OF $k^{\text{alanine}}_{Q,Q_{\text{cross}}}$ USING RAYSTATION

The relative effectiveness $\overline{\eta}_{\text{alanine}}$ of the local fluence distribution is computed in the Monte Carlo platform of the treatment planning system (TPS) RayStation v5.99.50 and scored at each voxel of the dose cube where the calculation of $\overline{\eta}_{\text{alanine}}$ is requested by the user.

This calculation is performed inline as the ratio of two numerical integrations:

$$\overline{\eta}_{\text{alanine}} = \frac{\sum_{i=1}^{n_{\text{hist}}} \sum_{j=1}^{n_i} \left[s_{ij} \times \left(\frac{S_{\text{el}}}{\rho}\right)_{\text{ala}} (E,Z) \times \eta_{\text{alanine}}(E,Z) + \eta TE_{ij} \right]}{\sum_{i=1}^{n_{\text{hist}}} \sum_{j=1}^{n_i} \left[s_{ij} \times \left(\frac{S_{\text{el}}}{\rho}\right)_{\text{alanine}} (E,Z) + TE_{ij} \right]} \tag{11}$$

where s_{ij} is the track length of each charged particle j crossing the voxel during history i and a track end contribution occurs whenever a particle reaches the transport energy cut-off E_{cut} within the scoring voxel:

$$TE_{ij} = \frac{E_{\text{cut}}}{\rho V_{voxel}} \tag{12}$$

$$\eta TE_{ij} = \frac{\int_0^{E_{\text{cut}}} \eta_{\text{alanine}}(E,Z) dE}{\rho V_{\text{voxel}}} \tag{13}$$

In the Monte Carlo TPS, Equation (11) was implemented by scoring the necessary quantities in-line during the simulation. For proton energies above about 20 MeV the nominator and denominator of Equation (11) were evaluated and accumulated at the midpoint kinetic energy at voxel traversals. Below 20 MeV a special track-end stepper procedure is employed where the energy loss is divided into 90 logarithmic energy loss steps down to 20 keV kinetic energy. The same accumulation was performed at each energy loss step. Finally, a contribution obtained by integrating numerically from 20 keV down to 1 keV is accumulated. It should be noted that the track-end procedure described above also accounts for possible voxel boundary crossings. The current version only considers protons (primary and secondary). A future version will also consider other secondary charged particles such as deuterons and alphas.

ICRU Report 49 [10] presents the most comprehensive set of stopping power data available in literature. However, no stopping power data for pure alanine and alanine pellet composition are reported. The Bragg's additivity rule using to compute stopping powers does not account for the influence of chemical binding effects. Based on the report published by the NPL in 2006 [9] the mass collision stopping power in pure alanine and in the alanine pellet material were computed.

For the calculation of the relative effectiveness a look-up table for protons based on the Hansen-Olsen model [11], lately revisited by Herrmann [4], was hardcoded in the Monte Carlo system. For each beam alanine dose weighted average relative effectiveness ($\overline{\eta}_{\text{alanine}}$) was scored in each voxel of the whole dose grid (3D distribution of $\overline{\eta}_{\text{alanine}}$). $k_{Q,Q_{\text{cross}}}^{\text{alanine}}$ for the voxels of interest (those where pellets are positioned) are then calculated using Equation (10).

6 EXAMPLE OF DERIVATION OF ABSORBED DOSE TO WATER IN PROTON BEAM FOR AN END-TO-END TEST CASE

In this chapter we provide an illustrate an example of the derivation of absorbed dose to water in proton beam, $D_{\text{w},Q}^{\text{alanine}}$, from the ^{60}Co-reference value of absorbed dose to water, $D_{\text{w}}^{\text{Co}-\text{ref}}$, as provided by the NPL. We refer to one of the end-to-end tests performed at MedAustron and reported by Carlino *et al* [7]. This case concerns a single beam delivered to the head phantom in non-isocentric setup [7].

Table 4. D_w^{Co-ref}, $D_w^{pQ_{cross}}$ $(= D_w^{Co-ref}\, k_{Q_{cross},Q_0}^{alanine})$, $\overline{\eta}_{alanine}$, $k_{Q,Q_{cross}}^{alanine}$ and $D_{w,Q}^{alanine}$ for each of the 22 alanine pellets.

Pellet #	D_w^{Co-ref}	$D_w^{pQ_{cross}}$	$\overline{\eta}_{alanine}$	$k_{Q,Q_{cross}}^{alanine}$	$D_{w,Q}^{alanine}$
1	9.644	9.857	0.982	1.018	10.036
2	9.660	9.873	0.983	1.018	10.048
3	9.715	9.929	0.982	1.018	10.109
4	9.552	9.763	0.982	1.018	9.937
5	9.730	9.944	0.981	1.019	10.135
6	9.528	9.738	0.982	1.018	9.914
7	9.805	10.021	0.996	1.005	10.066
8	9.815	10.031	0.995	1.005	10.077
9	9.793	10.009	0.996	1.004	10.053
10	9.704	9.918	0.996	1.005	9.963
11	9.814	10.030	0.996	1.005	10.075
12	9.762	9.977	0.991	1.009	10.063
13	9.771	9.986	0.991	1.009	10.074
14	9.788	10.004	0.991	1.009	10.091
15	9.642	9.854	0.991	1.009	9.940
16	9.916	10.134	0.991	1.009	10.224
17	9.819	10.035	0.994	1.006	10.095
18	9.840	10.057	0.994	1.006	10.114
19	9.817	10.033	0.994	1.006	10.092
20	9.757	9.972	0.995	1.006	10.027
21	9.793	10.009	0.994	1.006	10.066
22	9.842	10.059	0.994	1.006	10.115

Table 4 presents for each of the 22 alanine pellets the ^{60}Co-reference value of absorbed dose to water, D_w^{Co-ref}, as provided by the NPL, the pQ_{cross}-reference value of absorbed dose to water, $D_w^{pQ_{cross}}$, determined as the product of D_w^{Co-ref} and $k_{Q_{cross},Q_0}^{alanine}$, $\overline{\eta}_{alanine}$ computed by the TPS according to Equation (11), $k_{Q,Q_{cross}}^{alanine}$ derived as in Equation (10) and the absorbed dose to water in proton beam, $D_{w,Q}^{alanine}$, obtained according to Equation (6).

In Figure 5 the ^{60}Co-reference value of absorbed dose to water, D_w^{Co-ref}, as provided by the NPL and the absorbed dose to water in proton beam $D_{w,Q}^{alanine}$ are shown.

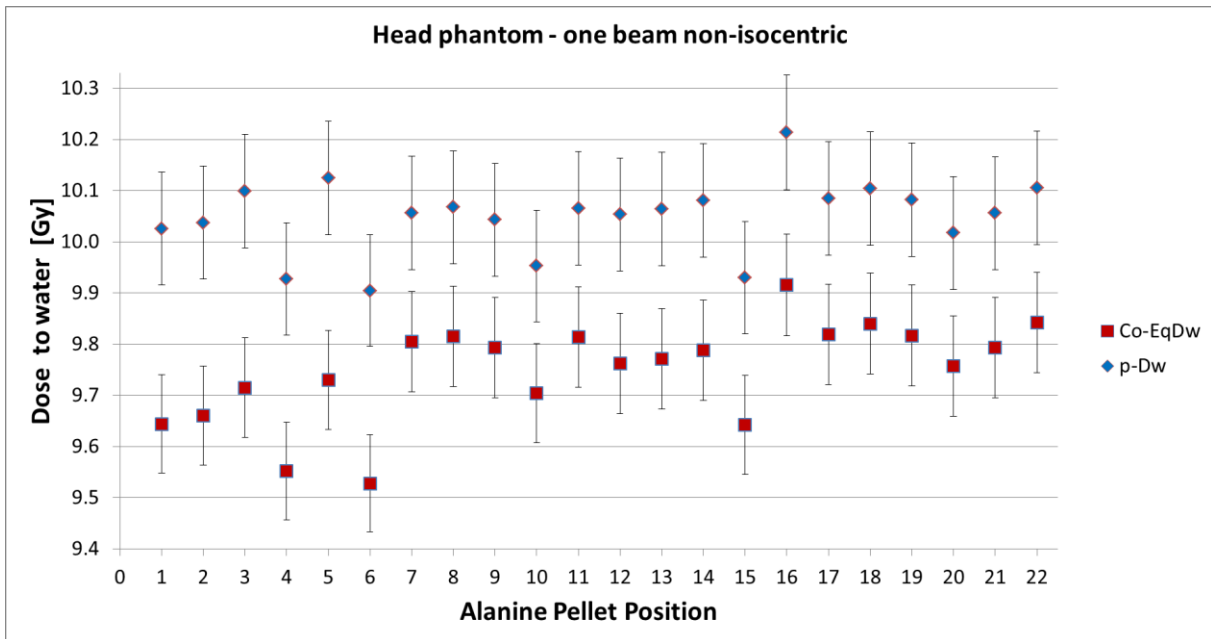**Figure 5.** ^{60}Co-reference value of absorbed dose to water, $D_{\mathrm{w}}^{\mathrm{Co-ref}}$, as provided by the NPL and the absorbed dose to water in proton beam, $D_{\mathrm{w},Q}^{\mathrm{alanine}}$, for the alanine pellets irradiated in the head phantom. The error bars represent standard uncertainties.
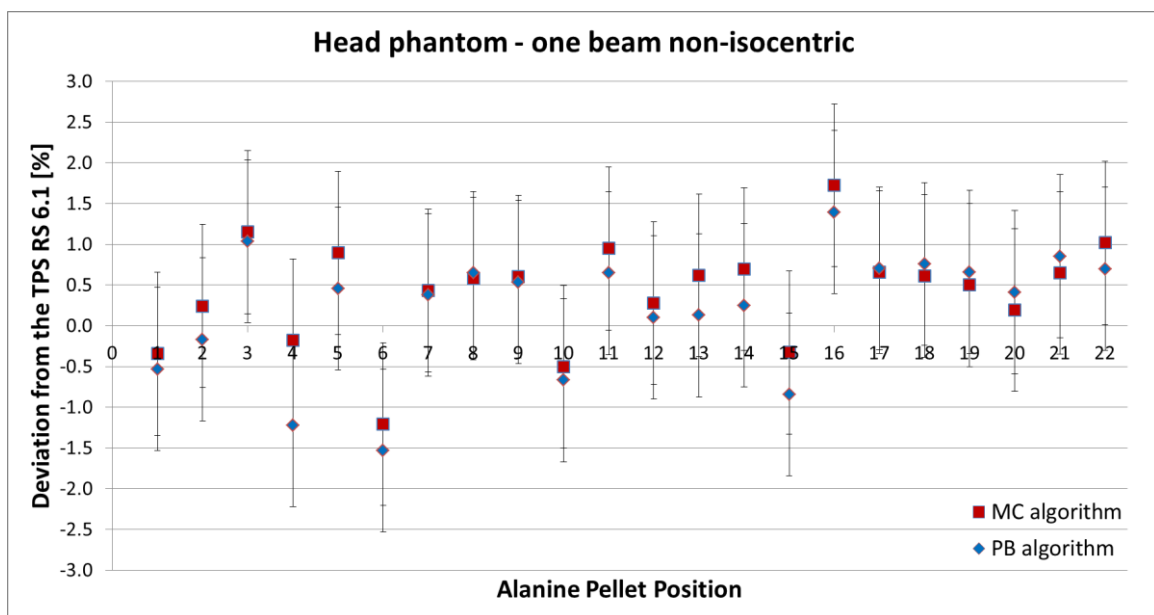

Figure 6: Relative differences between absorbed dose to water in proton beam $D_{\mathrm{w},Q}^{\mathrm{alanine}}$ derived from alanine and planned absorbed dose to water with the TPS. Blue symbols represent the comparison for the plan computed with the pencil beam algorithm and red symbols the comparison for the plan computed with the Monte Carlo algorithm.

In Figure 6 the deviations of the absorbed dose to water in proton beam $D_{\mathrm{w},Q}^{\mathrm{alanine}}$ and the planned absorbed dose to water with the TPS are shown.

The deviations of the measured doses with the dose computed with both algorithms are all within ±2%. For the pencil beam algorithm, the average deviation of is 0.4 ± 0.6 % while for the Monte Carlo algorithm it is 0.2 ± 0.7 %.

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